UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

June 7, 2012

MEMORANDUM

Subject:	Name of Pesticide Product:	EFFIPRO® PLUS TOPICAL SOLUTION FOR DOGS
	EPA Reg. No. /File Symbol:	2382-RIO
	DP Barcode:	DP 398344
	Decision No.:	459013
	Action Code:	R310
	PC Codes:	129032 (Pyriproxyfen: 2.9%)
		129121 (Fipronil: 9.7%)
From:	Byron T. Backus, Ph.D., Toxicologist	Byron T. Backus June 7, 2012
	Technical Review Branch	
	Registration Division (7505P)	M Hasler Team Leader, Toxicology
To:	Bonaventure Akinlosotu/Richard Gebken RM 10	
	Insecticide Branch	
	Registration Division (7505P)	
Registrant:	VIRBAC AH, INC.	

FORMULATION FROM LABEL:

Active Ingredient(s):	by wt.
129121 Fipronil	9.7%
129032 Pyriproxyfen	2.9%
Other Ingredient(s):	87.4%
TOTAL	100.0%

ACTION REQUESTED: The Risk Manager requests:

"For your review: R310. MRID 48696916; for a Fipronil + Pyriproxyfen containing Spot-On for dogs. Submits prod chem., tox, efficacy and CAS data…"

BACKGROUND:

The material received for review includes a proposed label, indicating the product is packaged in single-use applicators (1, 3, 6 or 36 applicators per package). Dosage rates are stated to be 0.023 fl. oz. (0.67 mL) "for small dogs and puppies 8 weeks old or older and up to 22.9 lbs," 0.045 fl. oz. (1.34 mL) for dogs weighing 23-44.9 lbs, 0.091 fl. oz. (2.68 mL) for dogs weighing 45-88.9 lbs, and 0.136 fl. oz. (4.02 mL) for dogs weighing 89-132 lbs. The product is to be applied no more frequently than once a month ("Effective monthly control of fleas and ticks," and "Once monthly application." There is a data matrix (dated December 20, 2011) which cites 12 studies to satisfy the companion animal safety data requirement (MRIDs 43444905, 43577711, 43863802, 43121110, 43121111, 45620507, 43396408, 43612601, 44900902, 44900903, 42178309, and "new submission" [presumably the material in MRID 48696916, which consists of summaries of several previously reviewed companion animal safety and other studies; OPPIN indicates no studies have been submitted for 2382-RIO] from Virbac.

COMMENTS AND RECOMMENDATIONS:

1. The following are review summaries of the eleven studies (the 12 indicated above less the material in MRID 48696916) that have been cited to satisfy the 870.7200 data requirement to support the registration of 2382-RIO.

- MRID 43444905: Schwartz, E. (1994) Domestic Animal Safety Study of RM1601C Topical Spray (Frontline Spray Treatment) in Juvenile Dogs: Lab Project Number: 94423: PS-232DAS. Unpublished study prepared by White Eagle Toxicology Labs. 171 p. [according to OPPIN the products supported by this study are 65331-1 and 65331-EUP-1; DERs for this study are in TXRs 0011677 and 0011764; Groups of 4 or 6 beagles (~8 weeks old) per sex received single applications of RM 1601C Topical Spray [0.25% w/v fipronil = 0.29% w/w fipronil] at dosages of 6 mL/kg (1X recommended dose) or 30 mL/kg (5X). A control group of 4/sex was treated with the vehicle at 30 mL/kg. This study was upgraded to acceptable in TXR 0011764].

- MRID 43577711: Walker, K. (1995) Discussion in Support of Bridging Domestic Animal Safety Data on Frontline Spray Treatment to Frontline Spot Treatment Data Package. Unpublished study prepared by Rhone Merieux, Inc. 6 p. [According to OPPIN the product supported is 65331-EUP-E; this is not an actual study, but an argument as to why there is justification for linking the spot-on product containing ~10% fipronil to the data base of an existing product (Frontline® Spray Treatment, 0.25% w/v fipronil)].

- MRID 43863802: Powell, L.; Paffett, R. (1995) Domestic Animal Safety Study by Topical Administration to Dogs: Fipronil Spot Treatment (RM 1601E): Lab Project Number: MRX 23/950406. Unpublished study prepared by Huntingdon Research Centre, Ltd. 219 p. [According to OPPIN the product supported was 65331-EUP-E; from TXR 0051187: "...4 male and 4 female pure-bred beagle dogs (approximately 10 weeks of age) were administered a single topical treatment of RM1601E/62 (9.7% fipronil) at either 1X, 3X or 5X the recommended dose (0.133 mg/kg/spot) once every month for a total of 6 treatments... 4 male and 4 female dogs served as a control group and were treated with the formulation vehicle at 5X the recommended dosage. A similar group served as an untreated control... The study demonstrated that RM1601E/62 (9.7% fipronil) has at least a 5X margin of safety

in dogs greater than 10 weeks of age. The product label should state that there may be temporary irritation after application." The study was classified as acceptable].

- MRID 43121110: Arnaud, J.; Consalvi, P. (1993) Assessment of Tolerance of a 0.25% RM 1601 Spray Formulation in Dogs at 3, 9, and 15 ml/kg When Applied 6 times to the Haircoat at 28 Day Intervals: Revised: Lab Project Number CLI138. Unpublished study prepared by Rhone Merieux, Inc. 69 p. [according to OPPIN the product supported by this study is 65331-EUP-1; a DER for this study is in TXR 0010923; groups of 3M & 3F beagle dogs were topically administered 6 treatments of 0.25% fipronil at dosages of either 0, 3, 9 or 15 mL/kg (0, 7.5, 22.5 and 37.5 mg fipronil/kg, respectively) at 28-day intervals. The proposed recommended dose for the 0.25% product was 3 to 6 mL/kg; 0.67 mL of a 9.7% fipronil product applied to a 5 kg dog would be equivalent to a dosage of 13 mg fipronil/kg. From TXR 0010923: "Classification: Unacceptable because: 1) the highest dosage level was not 5X the highest recommended dose; and 2) the study was not conducted in compliance with the GLP regulations].

- MRID 43121111: Arnaud, J.; Consalvi, P. (1993) Domestic Animal Safety: Assessment of the Tolerance of a 0.25% RM 1601 Spray in Nursing Puppies Administered Twice at a 28 Day Interval at a Dose Rate of 6 ml/kg: Revised: Lab Project Number CLI 180. Unpublished study prepared by Rhone Merieux, Inc. 32 p. [According to OPPIN the product supported by this study is 65331-EUP-1; a DER for this study is in TXR 0010923; a total of 27 male and 21 female nursing puppies (9 litters of either beagle, spaniel or griffon breeds) topically received two treatments of 0.25% formulation at a dosage of 6 mL/kg (proposed recommended dosage = 6 mL/kg) with 28 days between the treatments. The dams of the litters were treated at the same dosage. Twenty-six male and 15 females served as untreated controls. Six treated puppies, including four from the same spaniel litter, died before weaning and another died after weaning. Parvovirus was isolated from the spaniel litter. One control puppy died; there was no statistical difference in mortality between the groups. Growth rates were either comparable to or exceeded the applicable control group for the beagle and griffon breeds, but were lower for the spaniel (this lower growth rate may have been from the parvovirus infection). Classification: Unacceptable because: 1) the study was conducted with nursing rather than weaned puppies; 2) the highest dosage level was not at 5X the recommended dose; 3) the study was not conducted in compliance with GLP regulations].

- MRID 45620507: Godin, C.; Alva, R. (2000) ML-2,095,988 509T/Dog/Solution/Topical/Safety/ Tolerance/Reproduction, Reactions: Final Report: Lab Project Number: PR&D 0020201: WEL 99885: PR&D 00202. Unpublished study prepared by White Eagle Toxicology Laboratory. 123 p. [From OPPIN the product supported by this study is 65331-5; the review of this study is in TXR 5008387: In a special (reproductive) companion animal safety study a topical formulation containing 10% w/v fipronil and 9% w/v (S)-methoprene was administered at 0X (Group 1; sham-treated controls), 1X or 0.133 mL/kg (Group 2) and 3X or 0.399 ml/kg (Group 3) to groups of 12 adult female beagle dogs (bitches) prior to and during pregnancy, through parturition and to weaning of the puppies. The only dose-related effects observed in bitches were pink skin at the application site on days of treatment (recorded 15 times in Group 2, 37 times in Group 3), and pink skin at the application site on the day following treatment (3 times in Group 3). There was no indication of an adverse effect on any reproductive parameters (including gestation index, incidence of cesarean section, incidences of stillborn pups, incidences of pups dying between birth and weaning). There were no significant differences between puppies from the 3 groups with respect to physiological parameters (mean body

weights, mean rectal temperatures, mean respiratory rates, mean heart rates) measured on post-parturition days 14, 28 and 42 .

Although no dogs were dosed at 5X level, and no blood was taken for clinical chemistry and hematology measurements, the purpose of this study was to allow a label claim on breeding, pregnant and lactating bitches. TRB has previously reviewed a companion animal (dog) study for this formulation which included a 5X dosage group and measurements of clinical chemistry and hematology parameters. This study is classified as acceptable. The findings of this study are adequate to support the use of EPA Reg. Nos. 65331-3 and 65331-5 at the specified label use rates (varying according to the weight of dog) at 28-day intervals on breeding, pregnant and lactating bitches].

- MRID 43396408: Pennington, R.; Clymer, B. (1994) Study Report for the Target Animal Safety Evaluation of ECTO Flea and Tick Insecticide with IGR on Dogs: Lab Project Number: A-94-01-F701-007: 278-94-59: F701R09. Unpublished study prepared by CALV, Inc. & CRC. 28 p. [From OPPIN the product supported by this study is 67505-3; the review of this study is in TXR 0011565: 4 groups of mixed breed/beagle adults and puppies were exposed to 0, vehicle control (at 5X) or a formulation containing 45% permethrin and 5% pyriproxyfen at weekly intervals for a total of two applications. At 1X and above, slight to severe dermal reactions were observed. In the vehicle treated group 5/6 animals exhibited mild to severe dermal reactions which were as severe as in the 5X treated group. The study did not demonstrate a 3-5 fold safety factor between use as directed and dermal reactions].

- MRID 43612601: Pennington, R.; Kuhn, J. (1995) Report for the Target Animal Safety Evaluation of ECTO Flea and Tick Insecticide with IGR on Dogs: Lab Project Number: A-93-01-F701-027: 1617-94: F701R14. Unpublished study prepared by Ecto Development Corp. and Stillmeadow, Inc. 24 p. [From OPPIN the product supported by this study is 67505-3; the review of this study is in TXR 0011865: Adult dogs and puppies (1-2 subjects, ~3 months) 6/dose group were dosed once as control (untreated), 1X and 5X the label dosage rate of Ecto Flea and Tick Insecticide with IGR and followed for 31 days. No reactions to treatment were noted. The study demonstrated a 5X safety factor between use as directed and a dose level not resulting in toxicity or irritation. The study is classified as acceptable to support the use of this product (EPA Reg. No. 67505-3) on adult dogs (>6 months of age) only].

- MRID 44900902: Fabreguettes, C. (1998) Tolerance in 3 Month Old Puppies: Pyriproxyfen 2% Spot On For Dogs: Lab Project Number: CIT 15615TSC. Unpublished study prepared by Centre International de Toxicologie. 253 p. [From OPPIN the product supported by this study is 2382-RTU; Pyriproxyfen (2%) was topically applied to groups of three male and three female beagle dogs (3 months old; mean body weight of males 4.4 kg; females 3.9 kg) for two periods of three consecutive days each (days 1, 2, and 3 and then days 19, 20 and 21) at 0.6 mL (1X), 1.2 mL (2X), and 1.8 mL (3X) of the recommended therapeutic dose level, followed by a 15-day observation period. Controls were treated with 1.8 mL of excipient. No animals died during the study and there were no treatment related clinical signs. No changes in body weight, food consumption, water consumption, hematology, clinical chemistry, or urinalysis were treatment related. Electrocardiographic and ophthalmological examinations did not reveal any abnormalities in the treated animals. Microscopic examination did not reveal any treatment-related effects. Classification: Unacceptable; Deviations include not testing six animals/sex/group, and not testing at a dose of 5X].

- MRID 44900903: Fabreguettes, C. (1999) Tolerance in 1 Month Old Puppies: Pyriproxyfen 2% Spot On For Dogs: Lab Project Number: CIT 15644TSC. Unpublished study prepared by Centre International de Toxicologie. 194 p. [From OPPIN the product supported by this study is 2382-RTU; Pyriproxyfen 2% was topically applied to groups of three male and three female beagle dogs (1 month old) for two periods of three consecutive days (days 1, 2, and 3 and then days 19, 20 and 21) at 0.6 mL (1X) and 1.8 mL (3X) of the recommended therapeutic dose level, followed by a 15-day observation period.. Controls were treated with 1.8 mL of excipient. No animals died during the study and there were no treatment related clinical signs. Body weight gain was slightly reduced in treated animals, but not to statistically significant levels. Changes in hematology and clinical chemistry parameters were sporadic and did not appear to be related to treatment. Electrocardiographic and ophthalmological examinations revealed no abnormalities in the treated animals. Macroscopic and microscopic examination revealed no treatment related changes, although serous contents were observed in the abdominal cavity in 1/6 animals in the low dose group and 4/6 animals in the high dose group (but not in any control animals). The product labeling indicates that the dose is 0.021 fl. oz or 0.6 mL, and the application instructions state that the product should be reapplied every three months and should not be applied to puppies less than 1 month old. In this study the product was applied at 1X and 3X dose levels once per day for three consecutive days and again for another 3-day period 19-21 days after the first treatment. Classification: Unacceptable; Deviations include not testing six animals/sex/group, and not testing at a dose of 5X].

- MRID 42178309: Chapman, E. (1991) S31183: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 52 Weeks (Sumilarv Technical Grade): Lab Project Number: 91/0776. Unpublished study prepared by Life Science Research Ltd. 320 p. [Dose levels tested: 0, 30, 100, 300 and 1000 mg/kg/day in the diet for 54 weeks; study demonstrates a low level of toxicity associated with chronic exposure to Pyriproxyfen; the dietary NOEL was 100 mg/kg/day].

2. After comparing the CSFs for 2382-RIO and 65331-3, TRB concludes that the studies cited by the registrant to satisfy the 870.7200 data requirements adequately support the use of 2382-RIO at the indicated dosage rates (0.023 fl. oz. or 0.67 mL on dogs up to 22.9 lbs; 0.045 fl. oz. or 1.34 mL on dogs 23-44.9 lbs; 0.091 fl. oz. or 2.68 mL on dogs 45-88.9 lbs; 0.136 fl. oz. or 4.02 mL on dogs 89-132 lbs) on adult dogs and puppies of 8 weeks of age and older on a once-a-month (or every 4 weeks) basis.

3. TRB also concludes that because of the presence of 2.9% pyriproxyfen in 2382-RIO the study in MRID 45620507 cannot be used to support the use of 2382-RIO on breeding, pregnant and/or lactating bitches [although this claim does not appear on the proposed label dated December 14, 2011]. Labeling must then also include the statement: "Consult a veterinarian before using this product on debilitated, aged, pregnant or nursing animals" as indicated in PR Notice 96-6.